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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/649,527	08/28/2000	Sean C. Semple	INEXP006US	8470

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 03/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/649,527	Applicant(s) SEMPLE ET AL.	
	Examiner Dave Nguyen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4-6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Claims 1-21 are pending.

Applicant's species election without traverse of DODMA, PEG-lipid and polypeptides for the type of antigenic molecules in the response filed 1/11/01 is acknowledged.

After a further consideration of prior art, the species DODAP in the form of cationic lipid has also been rejoined and thereby will be examined along with the elected species of DODMA.

Elected claims 1-21, to which the following grounds of rejection remain and/or are applicable, are pending.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunostimulatory composition comprising a nucleic acid polymer encapsulated in a lipid particle comprising a cationic lipid, wherein the nucleic acid lacks an immunostimulatory CpG motif and has no detectable immune response in a mammal in the absence of the lipid particle, does not reasonably provide enablement for any other nucleic acid polymer that exhibit no detectable immunostimulatory activity when present in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification (pages 48, 49 and 53) coupled with the prior art of record teach that DNA are immunogenic when having a CpG motif. However, the claim embraces the making of any nucleic acid polymer that itself does not exhibit any detectable immunostimulatory activity when present in a mammal. With respect to this claimed embodiment, the specification only provide sufficient guidance and evidence to show that the nucleic acid polymer INX-6300 does not exhibit NK activity when present in a murine model. However, on the basis of prior art 's teaching the evidence provided by the specification, it is not apparent how the lack of NK activity against one specific DNA polymer of INX-6300 in a murine model can be reasonably extrapolate to the making of any other nucleic acid polymer that must exhibit no detectable immunostimulatory activity when present in any mammal including human, especially when unmethylated CpG motifs are commonly present in plasmid DNA. In

view of the foregoing reasons, it is not apparent how a skilled artisan, without any undue experimentation, makes and use the entire breach of the nucleic acid polymers as claimed in claim 15, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 11, 17 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The breadth of the claims is not definite because the phrase "selected from the among " or "selected from among" is not a proper Markush language. A standard and proper Markush language is either "selected from the group consisting of A, B, and C" or "A, B, or C". Thus, it is not apparent as to what is applicant's indented scope of the claim when using "selected from the among" or "selected from among". Clarification is requested. Note also that "the among" is grammatically incorrect.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuation) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht,* 168 USPQ 293 (CCPA 1971). The parent application, 09/078,954, filed May 14, 1998, does not provide written support for the utility of any composition comprising a nucleic acid polymer and any cationic lipid within the context of immune-adjuvant for inducing an useful immune response against any desire molecule. While the '954 application provides sufficient guidance and teachings for the making of a DNA delivery composition comprising a cationic lipid and a DNA nucleic acid polymer, such description and/or contemplation of the making of DNA/cationic lipid composition for

the purpose of using the composition simply as a DNA delivery composition is not the same as claiming now the **new property** and/or **new method** of any cationic lipid/DNA containing composition so as to induce a useful immune response against any desire antigen. Therefore, the parent application '954 application does not contain an adequate support of description the new property of immunostimulatory activity exhibited by any cationic lipid/DNA complexes which are essential for the practice of the claimed invention of this instant application, therefore priority for the claims readable on the conception of making and use of cationic lipid/DNA complexes as **immnostimulatory compositions within the context of adjuvants and/or inducer of an immune response** can only be established on the filing date of this instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-2, 6, and 20 are rejected under 35 U.S.C. 102(e) or 102(b) as being anticipated by Felgner *et al.* (US Pat No. 5,703,055), as evidenced by Bei *et al.* (J. Immunotherapy, 21, 3, pages 159-169, 1998)

The claims are readable on a method of employing any cationic amphiphile/biologically active molecule (DNA, RNA, polypeptides) contained composition regardless of the structure of the amphiphile and/or DNA so as to stimulate an immunostimulatory activity in a mammal. The '055 patent discloses a method for generating an immunostimulatory activity in a mammal by employing a cationic lipid/DNA complex, wherein said complex comprises a transduced vector or a polynucleotide expressing an antigen and any known cationic lipid/co-lipid complex, *e.g.,* DOTAP, columns 25 and 26. Delivery of the complex to tumor cell is disclosed on column 19, lines 40-45 and column 21, lines 21-26. Felgner *et al.* teach that "the polynucleotide material delivered to the cells *in vivo* can take any number of forms" (column 10). Suitable promoters, *e.g.*, RSV, SV40, and CMV, are disclosed on column 10. The polynucleotides can be delivered by

injection to the interstitial space of tissues of the animal body, including those of muscle, skin, brain, lung, and connective tissues (see column 13). More specifically, the '055 patent teaches that "the parenteral route of injection into the interstitial space of tissues is preferred, although other parenteral routes, such as inhalation of an aerosol formulation, may be required in specific administration, as for example to the mucous membranes of the nose, throat, bronchial tissues or lungs" (column 24). Felgner *et al.* disclose that "the polynucleotides may be injected into muscle or skin using an injection syringe...or...using a vaccine gun" (column 20). Regarding the DNA injection methods using a cationic lipid, Felgner *et al.* teach many suitable liposome forming cationic lipid compounds for use in the transient gene therapy method are described in the literature and available commercially (column 26). Specific examples demonstrating an antibody immune response against an antigen are disclosed in Examples 7-16 (tail vein injections, direct injection into the muscle, intratracheal and liver injections). Methods employing intravenous injections of a cationic lipid/DNA complex to deliver biologically active molecules including an interferon gene to human patients are disclosed at column 18, first paragraph.

Since the cationic lipid/DNA complexes and/or materially method steps of Felgner are identical to that of the claims of this instant application, and given the factual evidence shown by the Bei reference which indicates that cationic liposomes formulation (DOTAP) does stimulate immune responses and are themselves immunoadjuvant (entire document, especially the abstract), the cationic lipid/DNA complexes including the DOTAP lipid/DNA composition of Felgner *et al.* must inherently exhibit the property of immunostimulatory activity in a mammal.

Claims 1-3, 6, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by either Freimark *et al.* (The J. of Immunology, Vol. 160, pp. 4580-4586, 1998) or Ishi *et al.* (AIDS Res. And Human Retroviruses, Vol. 13, NO. 16, 1997).

The claims are readable on a method of employing any cationic amphiphile/biologically active molecule (DNA, RNA, polypeptides) contained composition regardless of the structure of the amphiphile and/or DNA so as to stimulate an immunostimulatory activity in a mammal. Both Freimark *et al.* and Ishi *et al.* (entire documents) teach identical compositions and method steps as recited in the claims. With respect to CpG motifs that are naturally present in plasmid DNA that were made from bacteria, see Table I of Freimark *et al.* for factual evidence.

Claims 1-3, 5, 9-14, 16, 20, 21 are rejected under 35 USC 102(a) or 102(e) as being anticipated by Krieg *et al.* (US Pat No. 6,207,646).

The essential feature of the presently pending claims is that any cationic lipid including can be used for a method of inducing an immune response when used in combination with a nucleic acid polymer including those containing CpG motifs which themselves are also immunostimulatory nucleic acid molecules. Krieg *et al.* teach that cationic lipid carriers (column 12, lines 25-34) can be employed in combination with a CpG motif containing nuleic acid polymer as immunostimulatory nucleic acid complex and with an antigen when employed for induction of an immune response to a target antigen. The 646 patent teach the same throughout the disclosure (particularly columns 29-35, columns 61-64).

Absent evidence to the contrary, the compositions and the methods disclosed in Krieg *et al.* have all of the properties cite in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-14, and 16-21 are rejected under 35 USC 103 as being unpatentable over any of Felgner *et al.*, Freimark *et al.* and Ishi *et al.*, taken with either Meers *et al.* (US Pat No. 6,143,716) or Wheeler *et al.* (US Pat No. 5,976,567), and further in view of applicant's admission over the prior art on pages 7 and 11 of the specification.

The rejection of the base claims as being anticipaged by any of Felgner *et al.*, Freimark *et al.* and Ishi *et al.* is applied here as indicated above. To the extent that the references do not teach further incorporations of known components (see pages 7 and 11 of the specification, for example) for additive effects, *e.g.*, CpG containing motifs with proper flanking residues that contributes to the immunostiumulatory effects, steric barrier lipid (PEG-lipid), drugs, cytotoxic agents, modified DNA with phosphodiester bonds, and/or recombinant antigen, or antigen encoded plasmids, it would have been obvious for one of ordinary skill in the art as a matter of design choice, of minor modifications, or of a combination effect, to employ any and/or all other components are recited in the claims, *e.g.*, CpG containing motifs with proper flanking residues that contributes to the immunostiumulatory effects, steric barrier lipid (PEG-lipid), drugs, cytotoxic agents, modified DNA with phosphodiester bonds, and/or recombinant antigen, or antigen encoded plasmids in the immunogenic compositions of any of the primary references. One of ordinary skill in the art would have been motivated to employ known immunostimulatory and/or therapeutic enhancing materials in the prior art so as to enhance addictive effects of the compositions taught in the primary references. Note that Krieg (WO 96/02555) as exemplified on page 7 of the specification, does teach the concept of adding known immunostimulatory materials including CpG motif containing oligos and/or recombinant antigens to known plasmid DNA vaccines is well established in the prior art of record. In addition, note also that Meers *et al.* teach on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.*, drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal.

The skilled artisan would also have been motivated to employ any known cationic lipid including DODMA and DODAP/PEG-lipid/DOPE as the lipid of choice because not only the primary references teach that cationic lipids are effective immuno-adjuvants, Wheeler *et al.* (column 50, example 26) and Meers *et al.* also teach that DODMA and DODAP/PEG-lipid/DOPE, respectively, are also effective as a vector for delivering and expressing any desire DNA in cells of a mammal. Note also that Meers *et al.* teach on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.*, drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal. Thus, an addition of well-recognized immune-stimulating agents including those of protein drugs to the teachings provided by the combined cited references would

have been minor modifications so as to provide addictive or combination effects, and thereby, would have been obvious to one skilled in the art at the time the invention was made.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-3, 5-14, and 16-21 are rejected under 35 USC 103 as being unpatentable over Krieg *et al.* (US Pat No. 6,207,646), taken with either McCluskie *et al.* (Critical Reviews in Immunology, 19, pp. 303-329, 1999) or Bei *et al.* (J. Immunotherapy, 21, 3, pages 159-169, 1998), and further in view of either Wheeler *et al.* (US Pat No. 5,976,567) or Meers *et al.* (US Pat No. 6,143,716).

The essential feature of the presently pending claims is that any cationic lipid including can be used for a method of inducing an immune response when used in combination with a nucleic acid polymer including those containing CpG motifs which themselves are also immunostimulatory nucleic acid molecules. Krieg *et al.* teach that cationic lipid carriers (column 12, lines 25-34) can be employed in combination with a CpG motif containing nuleic acid polymer as immunostimulatory nucleic acid complex and with an antigen when employed for induction of an immune response to a target antigen. The 646 patent teach the same throughout the disclosure (particularly columns 29-35, columns 61-64).

Krieg does not teach specifically that the liposomal vesicles contain a cationic lipid, nor does Krieg teach DODMA or DODAP and/or PEG-lipid as stabilizer for the nucleic acid delivery complexes.

However, at the time the invention was made, Bei *et al.* (entire document, especially the abstract) and McCluskie *et al.* (page 307 through page 308) do teach that cationic lipids, which themselves are effective conventional carriers for enhancing the delivery and expression of a target nucleic acid polymer, can also be used as effective adjuvant for the purpose of inducing an immune response against a target antigen.

In addition, Wheeler *et al.* and Meers *et al.* do teach that DODMA (column 50, example 26) and DODAP/PEG-lipid/DOPE (columns 8 and 9), respectively, also also effective carriers for delivering and expressing any desire DNA molecule in a mammal.

One of ordinary skill in the art would have been motivated to have employed a cationic lipid including DODMA or DODAP in the method of Krieg so as to enhance an immune response against a target antigen. One of ordinary skill in the art would have been motivate to employ a cationic lipid as an adjuvant because Bei *et al.* (entire document,

especially the abstract) and McCluskie *et al.* (page 307 through page 308) do teach that cationic lipids, which themselves are effective conventional carriers for enhancing the delivery and expression of a target nucleic acid polymer, can also be used as effective adjuvant for the purpose of inducing an immune response against a target antigen. The skilled artisan would also have been motivated to employ any known cationic lipid including DODMA and DODAP/PEG-lipid/DOPE as the lipid of choice because not only the combined cited references teach that cationic lipids are effective immuno-adjuvants, Wheeler *et al.* and Meers *et al.* also teach that DODMA and DODAP/PEG-lipid/DOPE, respectively, are also effective as a vector for delivering and expressing any desire DNA in cells of a mammal. Note also that Meers *et al.* teach on column 9 that additive components that are known to exhibit a therapeutically enhancing effects, *e.g.,* drugs, protein drugs, peptide drugs, can be used in a plasmid/DNA complexes so as to provide therapeutically addictive effect in a treated mammal. Thus, an addition of well-recognized immune-stimulating agents including those of protein drugs to the teachings provided by the combined cited references would have been minor modifications so as to provide addictive effects, and thereby, would have been obvious to one skilled in the art at the time the invention was made.

Thus, the claimed invention as a whole was *prima facie* obvious.

Krieg (US Pat NO. 6,218,371) is also cited to support the fact that combination use of immunotherapeutic nucleic acid polymers containing unmethylated CpG motifs, cytokines, and cationic lipids are well established in the prior art.

Mok *et al.* (Biochimica et Biophysica Acta, Vol. 1419, No. 2, pp. 137-150) teach that it is conventional in the prior art to employ SPLP composed of DOPE, cationic lipid (DODMA) and PEG-Cer as vectors for delivering nucleic acid molecules to a target cell *in vivo.*

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024.**

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

DAVE T. NGUYEN
PRIMARY EXAMINER